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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/679,951	10/06/2003	Thomas Luther	2923-571	3589

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EXAMINER	
HOWARD, ZACHARY C	

ART UNIT	PAPER NUMBER
1646	

NOTIFICATION DATE	DELIVERY MODE
08/09/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PTO-PAT-Email@rfem.com

Office Action Summary	Application No.	Applicant(s)	
	10/679,951	LUTHER ET AL.	
	Examiner	Art Unit	
	Zachary C. Howard	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 May 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *39-42,45-49,56-59 and 61* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *39-42,45-49,56-59 and 61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 June 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 5/21/07 has been entered.

Status of Application, Amendments and/or Claims

The response of 5/21/07 has been entered in full. No claims are amended.

Claims 39-42, 45-49, 56-59 and 61 are under consideration in the instant application.

Maintained Objections and/or Rejections

Claim Rejections - 35 USC § 112, 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 39-42, 45-49, 56-59 and 61 are rejected under 35 U.S.C. § 112, first paragraph, because the specification while being enabling for a method of providing a prognosis for a patient with a breast tumor comprising measuring the ratio of uPAR del4+5 deletion variant to del2+3+4 in a tumor sample from said patient, does not reasonably provide enablement for a (1) a method for the detection of tumors associated with generation of uPAR deletion variants or (2) or a method of providing prognosis for a tumor-bearing patient. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. This rejection was set forth previously and maintained at pg 2-3 of the Advisory Action mailed on 3/6/07.

It is noted that claims 39-42 and 46, while not explicitly reciting that the method provides a prognosis, each broadly encompass a method wherein detection of the splice variant provides a prognosis for said tumor, particularly in view of dependent claim 45 (dependent from claim 39) which does specifically recite such an intended use. It is also noted that the only use set forth in the specification for a "method for the detection of tumors associated with the generation of at least one uPAR deletion variant" is for providing a prognosis for said tumors.

Applicants' arguments (5/21/07; pg 7-9) as they pertain to the rejection have been fully considered but are not deemed to be persuasive. Applicants' arguments are as follows. In the response, Applicants argue that the claims are fully enabled. Applicants submit a "Rule 132 Declaration of Dr. Bernd Mühlenweg" that presents "data obtained from the final report on the research project on which the present application is based" (pg 8). Applicants argue that the data presented with this Declaration shows that "mRNA expression analysis of the deletion variants uPAR-del4/5 and uPAR-del5 in comparison to wild type deletion variant uPAR-del2/3/4 in other types of cancer (in addition to breast)" and "a correlation between various tumor diseases and the splice variants uPAR-del4/5 and uPAR-del5" (pg 8). Applicants point to the high levels of del4/5 and del5 in ATCC cell lines derived from prostate, bladder and kidney carcinomas. Applicants further submit that uPAR-del5 has applicability as a tumor marker because the results of Figure 2 show that "uPAR-del5 mRNA can be detected with a high frequency in tumor cells (even if only with a low expression level)" (pg 8).

Applicants' arguments have been fully considered but are not found persuasive for the following reasons. The claimed invention encompasses methods of prognosis based on the detection of splice variants of the urokinase-type plasminogen activator receptor (uPAR) in tumor samples. The specification identifies two novel uPAR splice variants (del4 and del4+5); a third (del5) was identified in the prior art (del5) in a HeLa cell line (Casey et al, 1994. Blood. 84(4): 1151-1156; cited previously). Each variant is the result of an alternative splicing event that removes exon 4 and/or exon 5 from the mRNA encoding the uPAR protein. Applicants have associated a "high del4+5 versus del2+3+4 ratio with a high relapse frequency (Fig 21)" (see specification, pg 29, lines 20-21). The sample termed "del2+3+4" includes any variant with exon 2, 3, and 4 and therefore includes both wild type uPAR (also termed del-wt) and the variant del5. As taught at pg 708 of Luther et al, the same primer set amplifies "fragments either from the uPAR-wt and/or from the uPAR-del5 variants" (Luther et al, 2003. Thromb Haemost. 89(4): 705-717). The high relapse frequency was observed in patients afflicted with primary breast cancer; Figure 21 shows that patients with a ratio of uPAR-del4/5 to uPAR-2/3/4 of over 0.043 are more likely to have "disease recurrence" as opposed to "no disease recurrence" whereas patients with a ratio under 0.043 are more likely to have "no disease recurrence". In view of Applicants' working example, the claims are enabled for a method of providing a prognosis comprising obtaining a breast tumor sample by measuring the ratio of del4+5 cDNA versus del2+3+4 cDNA. However, this single working example does not provide enablement for the full scope of methods encompassed by Applicants' claims for the following reasons:

(1) Applicants' claimed methods encompass a method of prognosis for any form of tumor. Applicants working examples provide prognosis for a tumor from a single type of tissue (i.e., breast cancer) based on a single comparison of relative transcript levels. This is not sufficient to enable a broad genus of tumors from different tissue types. As set forth previously, it is well known in the art that splice variant expression "patterns of alternative splicing can be tissue, stimulus or disease specific" (see pg 586 of Brinkman et al. 2004. Clinical Biochemistry. 37: 584-594; cited previously). Further, Kalnina et al (2005) teaches, "The selection of alternative splice sites can be regulated in different manners: tissue specificity, developmental stage, physiological processes, sex determination, and in response to various stress factors" (pg 344 of Kalnina et al. 2005. Genes, Chromosomes and Cancer. 42: 342-357; cited previously). Furthermore, alternative splicing is frequently tumor-specific; Okumura et al (2005) found that "among these 31 examples, 21 showed apparent differences between the normal and tumor alternative splicing patterns in at least one tissue, with six showing a difference in all four tumor tissues examined (Table 1)" (pg 24 of Okumura et al. 2005. Biochemical and

Biophysical Research Communications. 334: 23-29; cited previously). Therefore, as set forth previously, it is unpredictable whether or not results similar to those found by Applicants for del4+5 in breast tumor would be found with other types of tumor. To enable the use of the claimed method for prognostic generalizations for all types of tumor, one of skill in the art would first need to engage in undue experimentation to determine whether or not expression of the del4+5 splice variant is correlated with prognosis in tumors from a variety of tissue types.

The Mühlenweg Declaration has been fully considered but is not sufficient to demonstrate that the claims are enabled for providing a prognosis for tumors from tissues other than breast tissue (i.e., cancers other than breast cancer). Part 1 of the Results section of the Declaration is titled, "Expression of uPAR-del4/5-mRNA in breast cancer tissues" and is accompanied by Figure 1 (pg 2-3). Part 1 concerns the prognosis (disease recurrence) based on analysis of uPAR-del4/5: wt-uPAR mRNA ratios (the mRNA is amplified as cDNA for analysis). As such, Part 1 parallels and supports the single working example shown in the specification as filed (as described above). Part 2 of the Results section of the Declaration concerns the ratio of uPAR-del5 to wt-uPAR. Neither Part 1 nor Part 2 provides support for providing a prognosis using uPAR-del4/5 to wt-uPAR mRNA ratios in other types of tumor. Part 3 (including Figure 3) of the Results section of the Declaration does concern "expression analyses of uPAR-del4/5 and -del5 in further carcinoma lines". Part 3 describes the expression level of each splice variant (del4/5 or del5) in comparison to "uPAR-FL" (which is stated to be "wild-type uPAR-2/3/4"). The results indicate that each splice variant can be detected in prostate, bladder, and renal cell lines in addition to breast cell lines. However, while these results demonstrate the expression level of the splice variants in particular tumor cell lines, these results are not sufficient to demonstrate that detection of said splice variants can provide a prognosis for a patient with a tumor from any type of tissue for the following reasons.

The relevant art teaches that tumor cell lines frequently have different gene expression patterns than primary tumor samples taken from patients. This differential gene expression results from the heterogeneity of tumor samples and the selection process for immortalized cells that can grow in culture (which a significantly simplified microenvironment from the complex microenvironment found *in vivo*). Lacroix et al, 2004 teaches "[c]ancer cells are genetically unstable...as compared to cells *in vivo*, they could undergo specific genotype/phenotype alterations resulting from long-term culture in simplified condition" (see pg 255 of Lacroix et al, 2004. Breast Cancer Research and Treatment. 83: 249-289). Kobaek-Larsen (2000) cautions, "Cell lines are highly selected cells, usually monocultures, which have the ability to grow *in vitro*. Furthermore, cell lines are far away from their origin, due to multiple cell divisions and animal passages. Therefore, tumor cell lines may not be representative of *in vivo* derived tumor cells. When working with cell lines, it is considered essential that the characteristics of the cell lines be examined and described in detail..." (see page 22 of Kobaek-Larsen et al, 2000. Comp Med. 50(1): 16-26; cited previously). As such, the results presented in the Declaration concerning expression of the splice variants in established tumor cell lines does not speak to the predictability of the expression of the splice variants in primary tumor samples. In view of the limited teachings of the specification and the relevant art, the skilled artisan could not predict whether the splice variants observed in the tumor cell lines are actually found in primary prostate, bladder, or renal tumor samples or whether the splice variants have simply arisen (or had their expression enhanced) as part of the genetic alterations that occur during the process of selecting the tumor cell line. It remains that the skilled artisan would need to first examine a representative number of primary samples from prostate, bladder and renal tumors to determine whether or not said tumors also exhibit the splice variants. Furthermore, the expression of the splice variants in the tumor cell lines does not speak to the predictability of providing a prognosis of the relevant tumor based on splice variant expression. There is no corresponding analysis, such as that provided in the specification for breast tumor samples, showing the likelihood of disease occurrence based on a specific ratio of splice variant expression. Therefore, even if such splice variants are expressed in one or more primary tumor samples, it remains that the skilled artisan, prior to practicing the claimed method, would need to analyze the ratio of expression in a representative number of primary tumor samples and determine whether the particular ratio correlated with a particular prognosis. The relevant art supports the necessity of such an analysis and that clinical studies are the standard for confirming the usefulness of splice variants in tumor diagnosis. Brinkman et al (2004) teaches, "A large number of cancer-related genes that exhibit alternative splicing have been characterized...[t]argeted clinical studies are in many cases required to confirm their usefulness in the diagnosis and/or monitoring of cancer" (see pg 587 of Brinkman et al, 2004. Clinical Biochemistry. 37: 584-594; cited previously). Finally, it is noted that each of the cell lines used in the analysis presented in the Declaration is from a "urological carcinoma" (as is stated on page 5) and provides no information regarding the myriad other forms of tumors, e.g. lung, skin, gastric, colon or brain tumors, each of which would be predicted by the skilled artisan (in view of the relevant art cited above) to have different patterns of gene expression and/or splicing.

(2) Applicants' claimed methods encompass diagnosis and prognosis by detection of any uPAR deletion variant, wherein at least one uPAR deletion variant is del5 or del4+5. However, Applicants have only provided a single working example consisting of a single analysis wherein a particular ratio (del 4+5 versus del 2+3+4) is correlated with a particular prognosis for a particular tumor (breast). In view of the teachings of the relevant art (cited above) regarding the unpredictability of splice variant expression in different diseases or conditions, the single analysis provided for del4+5 is not sufficient to enable the method for the deletion variant del5. In the response, Applicants argue that the results presented in the Declaration show uPAR-del5 mRNA can be detected in tumor cells with low expression but high frequency (pg 8, see quotation provided above). The Declaration provides results concerning the ratio of uPAR-del5 to uPAR-2/3/4/5 mRNA (amplified as cDNA) in primary tumor tissue in section 2 of the Declaration (pg 3-4; Figure 2). However, these results are not sufficient to demonstrate the predictability of using said ratio for prognosis. The ratio appears to range from ~0.4 % (.004) to ~0.8% with error bars extending from ~0.1% (.001) to 1.5% (.015). First, these numbers are significantly different from the cut-off point (.043) for prognosis for the ratio of uPAR-del4/5 to uPAR-2/3/4 found in breast tumor samples. The Declaration acknowledges that uPAR-del5 has a relatively low level expression.

However, the skilled artisan would not know what ratio would provide a prognosis of disease-free survival or disease recurrence. What is missing is a correlation between an observed ratio using uPAR-del5 measurements and a particular prognosis (disease-free survival or disease recurrence). As such, the results do no speak to predictability of using the ratio of uPAR-del5 to uPAR-2/3/4/5 for prognosis. The del5 splice variant may be expressed in all breast tumors at a low level with no correlation between expression levels and disease prognosis. Section 3 of the Results section of the Declaration discloses uPAR-del5 expression in prostate, bladder, renal and breast tumor cell lines. The results do not speak to the predictability of using uPAR-del5 for prognosis of other cell lines for the same reasons set forth for del4/5 above.

Furthermore, as set forth previously, Kotzsch (2005), in a paper titled "Prognostic relevance of uPAR-del4/5 and TIMP-3 mRNA expression levels in breast cancer" states that "[t]he expression levels of uPAR-wt and uPAR-del5 were not associated with prognosis" (pg 2763 and pg 2767 of Kotzsch et al, 2005. European Journal of Cancer. 41: 2760-2768; cited previously). As such, the relevant art supports the unpredictability in practicing a method of prognosis based on measurement of uPAR-del5.

In summary, the Mühlenweg Declaration has been fully considered but is not considered sufficient to overcome the rejection. The results presented in the Declaration are not sufficient to demonstrate that the specification as originally filed provides enablement for the full scope of the claims. Therefore, it is maintained that the teachings of the specification provide only a single working example encompassed by the claims and do not provide enablement for the full scope of the claims.

New objections and/or rejections

Specification

The disclosure is objected to because of the following informality:

The title of the invention, "PRODUCTION OF POLYCLONAL, MONOSPECIFIC ANTIBODIES AGAINST THE UPAR VARIANTS DEL4, DEL5 AND DEL4+5 AND THEIR USE FOR DIAGNOSTIC AND THERAPEUTIC PURPOSES" is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. Specifically, the title refers to the production and use of antibodies. However, the currently pending claims are solely directed to methods of use of nucleic acids (e.g., cDNA amplified from mRNA) from tumor samples to provide a prognosis.

Appropriate correction is required.

Claim Rejections - 35 USC § 112, 2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 42, 45, 47-49 and 59 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 42 recites the limitation "the amplification of the cDNA" in lines 1-2. There is insufficient antecedent basis for this limitation in the claim. Specifically, claim 42 depends from claim 39 and recites, "wherein the amplification of the cDNA is done by real-time RT-PCR amplification". However, parent claim 39 refers to a sample containing cDNA but does not refer to "amplification" of this cDNA.

Claim 45 recites the limitation "tumors" in line 2. There is insufficient antecedent basis for this limitation in the claim. Specifically, claim 45 depends from claim 39 but parent claim 39 only refers to a single "tumor".

Claims 47-49 depend from claim 45 and are rejected for depending from an indefinite claim.

Claim 59 recites the limitation "the amplification of the cDNA" in lines 1-2. There is insufficient antecedent basis for this limitation in the claim. Specifically, claim 59 depends from claim 56 and recites, "wherein the amplification of the cDNA is done by real-time RT-PCR amplification". However, parent claim 56 refers to a sample containing cDNA but does not refer to "amplification" of this cDNA.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachary C. Howard whose telephone number is 571-272-2877. The examiner can normally be reached on M-F 9:30 AM - 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nickol can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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